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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,931	08/02/2001	Debra L. Shade	1812 US	8818

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,931	SHADE ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8/2/01 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 U.S.C. § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing retinal ganglion cell death comprising administering an effective amount of ADNF as structurally defined by Brenneman et al (1998; IDS Ref # DR), does not reasonably provide enablement for treating unknown "damage"/ cells/ neurons with structurally uncharacterized proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification proposes a method of "treating retinal and/or optic nerve head damage with a "pharmaceutically effective dose" of ADNF. However, the sole disclosure provided in the specification is that "[r]etinal and/or optic nerve head damage can result from..." various neuropathies. It is noted that no specific neuropathological condition involving retinal neurons or the optic nerve is known in the art or disclosed in the instant specification, whose dysfunction is characterized by altered expression of ADNF, at the time of filing Applicants' invention.

First, the state of the art is such that problems encountered before assessing whether treatment with a "pharmaceutically effective amount" of ADNF reasonably occurs within the

CNS (i.e., including retinal ganglion) are that neuronal cell damage often results in cell death, and that "administration" of neurotrophic factors to treat neurons requires solutions to not only bypassing the blood-brain barrier when treating CNS disorders but to selectively target responsive cells, if known, with enough neurotrophic factor to elicit any response (i.e., through specific receptor binding).

Second, in order to practice the full scope of the invention, regeneration of the damaged axons in these neurodegenerative disease states are required, in order to keep the damaged neurons from dying. However, without functional synaptogenesis, there is no functional regeneration, and therefore, no expectation that degeneration can be effectively prevented, or that an "effective" treatment of "retinal and/or optic nerve head damage", as claimed, is possible. Regeneration does not occur either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, astrocytic scarring blocks axonal elongation, or because of misdirected axonal growth (e.g., see Jackowski, pgs. 309-310). In other words, neurons do not regenerate in the CNS (e.g., see Jackowski, pg. 305, last *pp*). In contrast, the instant description fails to provide any guidance on how to prevent damaged neurons from degenerating; nor how to assay such *in vivo*. For example, only the outer segment of photoreceptor cells can effectively be treated when damaged, versus any more severe type of retinal neuronal damage that results in cell death (see Rapp, pg. 971, Fig. 2); thereby, being consistent with the unpredictable state of the art as discussed above, in which no treatment is known in the art for treating any neuropathological condition that

encompasses "ischemic... neuropathies", "macular degeneration", etc. as described on page 3 of the specification, which again are all characterized by neuronal cell death.

Thus, because it is unknown what parameters are required to be assayed in order to determine when, or if, the instant invention is "effective" in treating any neuropathic degenerative condition characterized by cell death, because the instant specification discloses no *in vivo* assays for determining when, or if, the Applicant's invention works *in vivo* or when retinal ganglion neurons are actually "treated", because it is not known nor disclosed how the severity of symptoms (which are also not recited) are related to the efficacy of ADNF, and because it cannot be successfully extrapolated from the limited guidance provided within the instant specification whether the skilled artisan has successfully practiced Applicant's invention, the current claims merely constitute an invitation to experiment how to use the invention, in light of the unpredictable state of the art in treating dying neurons.

Lastly, the name "ADNF" alone (e.g., as it is defined on page 3 of the specification) encompasses any "analogue", "agents that upregulate endogenous ADNF", or any biologically functional equivalent of an ADNF- related polypeptide, which provides no structural and little functional characteristics for how to make the "ADNF" molecules required to practice the claimed method. In contrast, the specification fails to define what specific amino acids are critical for any ADNF-related function, or what minimal structural requirements are necessary to make the ADNF molecule/agent which retains the desired function of the instant invention. Therefore, the skilled artisan would reasonably expect that random mutations/modifications to

any ADNF protein (i.e., as encompassed by the current claim language) would result in an inactive ADNF protein, and therefore a method that does not work. For example, Rudinger states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger then states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Thus, one skilled in the art would not know how to make and use the ADNF component required to practice the instant method because any such random mutation/ modification manifested in an ADNF- related polypeptide would be predicted to adversely affect the three-dimensional conformation of the polypeptide, and therefore, the method itself, without requiring undue experimentation to determine otherwise.

Claim Rejections - 35 U.S.C. § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Gozes et al (WO 98/35042; IDS Ref # AN) .

Gozes et al teach treatment of "retinal neuronal degeneration" with pharmaceutically effective amounts of ADNF polypeptides (pg. 60, line 12; and pgs. 61-63), which is a "retinal and/or optic nerve head damage" (as also acknowledged on page 3 of the instant application); thereby, anticipating claim 1, as recited.

Conclusion

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
November 10, 2003